REMARKS

Formal Matters

Claims 69-87 were examined and rejected.

Claim 76 is amended. Support for the amendment is found at, e.g., page 3, lines 28-29.

No new matter is added.

Reconsideration of this application is respectfully requested.

Priority

According to the Application Data Sheet (ADS) filed in this application on November 5, 2007, this application is a continuation of an earlier continuation that claims the benefit of provisional applications 60/152,524, 60/151,114 and 60/108,029, filed on September 3, 1999, August 27, 1999, and November 12, 1998, respectively.

The Applicants submit that support for the method claimed in the instant application is found throughout each of the three provisional applications listed in the ADS. For example, cell based cAMP assays and peripheral blood leukocytes are described in: a) 60/152,524 at, for example, page 16, line 1 to page 20 line 10, page 14 line 23, page 5 line 22 and page 26, line 17 to page 28 line 19; b) 60/151,114 at, for example, page 15 line 11 to page 20 line 10, page 14 line 23, page 5 line 22 and page 26, line 17 to page 28 line 19; and c) 60/108,029 at, for example, page 15 line 11 to page 20 line 10, page 14 line 23 and page 5 line 22.

For the Examiner's convenience, 60/108,029, 60/151,114 and 60/152,524 are appended to this response.

Rejection of claims under 35 U.S.C. § 112, second paragraph

Claims 33-35 and 51-68 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. This rejection is applied to new claims 69-87, and respectively traversed.

Claim 76 is allegedly indefinite because the term "biological response" is unclear.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claim 76 is amended to recite "detecting a level of apoptosis produced by increasing cAMP levels".

The Applicants submit that the meaning of claim 76 is clear, and that this rejection of claim 76 should be withdrawn.

Claims 79 and 81 are allegedly indefinite because of the use of the term "relative to".

According to MPEP § 2173.05(b), a relative term that refers to an object that is variable may render a claim indefinite.

In this case, however, claims 79 and 81 recite "relative to SEQ ID NO:82" and, as such, those claims refer to an object, i.e., SEQ ID NO:82, that is *not* variable.

Since claims 79 and 81 refer to an object that is not variable (i.e., SEQ ID NO:82), the meaning of each of claims 79 and 81 is clear and, as such, this rejection of claims 79 and 81 should be withdrawn.

The Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is requested.

Rejection of claims under 35 U.S.C. § 101

New claims 69-87 are rejected under 35 U.S.C. § 101 as allegedly unsupported by a patentable utility. The Applicants respectfully traverse this rejection.

The Applicants initially note that the Examiner has not specifically rebutted the Applicants' prior arguments as set forth in the response of November 5, 2007, which makes it difficult for the Applicants to respond to this rejection in a meaningful way. Thus, if this rejection is to be maintained, the Examiner is respectfully requested to provide a specific rebuttal of the arguments presented in this response, as well as the Applicants' prior response.

Applicants request that the arguments presented in the response of November 5, 2007, be applied to this rejection. The remainder of this response addresses comments made by the Examiner on page 5 of the Office Action.

On page 5 of the Office Action, the Examiner indicates that TDAG would have a patentable utility if, in the future: a) the activity of TDAG were linked with a disease state and b) TDAG8's ligand

were characterized. Specifically, the Examiner states on page 5, lines 13-15. "The TDAG8 GPCR may have utility in the future, when it has been further characterized (e.g. its dysfunction or function correlated with a disease state) and its ligand characterized."

With respect to the Examiner's statement that TDAG8 would have patentable utility if its activity were linked to a disease state, the Applicants submit that the specification clearly states that TDAG8 is a human T-cell death receptor (page 3, lines 23-24) and that there is a strong correlation between apoptosis and TDAG8 (see page 3, line 28). The role of TDAG8 in T cell apoptosis was known before the Applicant's application was filed. Since T cell apoptosis is the process by which the human body rids itself of ineffective and potentially damaging immature T cells, and dysregulation of T cell apoptosis causes inflammatory diseases (e.g., inflammatory bowel disease [reviewed in Neurath et al, Trends Immunol. 2001 22:21-6] and lupus [see, e.g., Silvestris et al, Lupus. 2003;12:8-14], for example) as well as lymphoma (reviewed in Kacinski et al, Ann N Y Acad Sci. 2001 941:194-9), the Applicants believe that the correlation that the Examiner appears to require already exists. The association between TDAG8 and T cell apoptosis, as described in page 3 of the application, should be sufficient to provide utility to the claimed method.

With respect to the Examiner's statement that TDAG8 would have patentable utility if the ligand of TDAG8 were characterized, the Applicants note that it is a common misperception that orphan receptors, and by extension screening assays to identify compounds that modulate orphan receptors, have no utility. However, knowledge of a GPCR's natural ligand is simply not necessary for establishing a useful function for such a receptor. In fact, it is possible to know a receptor's function and develop and market pharmaceutical agents targeting it without any understanding of the natural ligand which activates it. For example, many opiates were identified and developed and the analgesic functionality of these compounds at the mu-opiate receptor was appreciated long before the first endogenous agonists of that receptor were discovered in 1975 (see Zadina et al., Ann NY Acad Sci. 1999; 897:136-44). Therefore, because orphan GPCRs have been characterized and found useful, even in the absence of a known endogenous ligand, Applicants submit that a method for identifying modulatory compounds for such functionally-characterized orphan GPCRs represents a specific, substantial "real world" use of the claimed invention. In view of the above, the Applicants respectfully submit that the Examiner's argument that TDAG8 has no utility because its natural ligand is not known carries no weight.

The Applicants submit that the claimed method has a utility that is credible, specific and substantial. Since no more is required to meet the requirements of 35 U.S.C. §101, this rejection should be withdrawn.

Rejection of claims under 35 U.S.C. § 112, first paragraph (utility)

Claims 33-35 and 51-68 are rejected under 35 U.S.C. §112, first paragraph, because they are rejected under 35 U.S.C. §101. This rejection is applied to new claims 69-87.

The Applicants respectfully submit that this rejection should be withdrawn along with the §101 rejection for the reasons outlined above.

Withdrawal of this rejection is requested.

Rejection of claims under 35 U.S.C. § 112, first paragraph (written description)

Claims 69-87 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not adequately described by the instant specification. The basis for these rejections relates in large part to the claims encompassing variants of human TDAG8. The question is whether such variants are adequately described in the specification. This rejection is respectfully traversed.

The Applicants again note that the Examiner has not specifically rebutted the Applicants' prior arguments in the response of March 11, 2009, which makes it difficult for the Applicants to respond to this rejection in a meaningful way. Thus, if this rejection is to be maintained, the Examiner is respectfully requested to provide a specific rebuttal of the arguments presented in the Applicants' prior response.

The arguments presented in the Applicants' prior response are set forth below. The Examiner is referred to the Exhibits were filed with the Applicant's prior response.

In response, the Examiner is respectfully directed to Fig. 2 of *Kyaw* (DNA Cell Biol. 1998 17: 493-500) which shows a pairwise alignment of the amino acid sequences of human TDAG8 and mouse TDAG8. *Kyaw* has been provided to the office in the Information Disclosure Statement filed on February 18, 2004. *Kyaw*'s Fig. 2 is shown below:

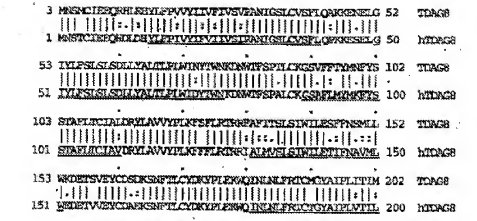

FIG: 2. Alignment of amino acid sequences of the mouse TDAG8 (top) and the hTDAG8 (bottom). Underlined sequences represent the seven putative transmembrane domains of the hTDAG8. The alignment presentation was done with BESTFIT in the GCG package.

According to Kyaw's results section, the mouse and human TDAG8 proteins are about 81% identical, which agrees with the Applicant's calculations. Since the claimed method can be performed with either of these proteins, or any hybrid protein that contains any combination of sequences from the mouse and human proteins, the Applicant submits that one of skill in the art would be able to envision a large number of operable variants of TDAG8.

Further, the Examiner is respectfully referred to:

a) page 2, lines 15 to page 3 line 11, of the instant specification, where the structure/function relationship of GPCRs is described;

b) page 27, line 27 to page 28, line 8, particularly, page 28, lines 5-8, where the amino acid polymorphisms in human TDAG8 are described;

c) page 28, lines 27-31 and Table I on page 42, where the specification provides guidance for making constitutively active mutants of TDAG8; and

d) the section starting on page 35, where a variety of methods for assaying GPCRs (which can be used to test variant proteins) are described in detail.

Also, as shown in Exhibit A, a search of NCBI's PubMed database reveals that there are well over 1275 journal articles, including 172 reviews, that have a publication date that precedes the priority date of the instant application (November 12, 1998) and contain the phrase "GPCR" OR "G protein-coupled receptor" in the abstract. Thus, at the priority date of the instant application, GPCR proteins were a subject of significant interest in the scientific community. The art in which the subject TDAG8 protein belongs was therefore highly developed at the priority date of the instant application.

For example, at the priority date of the instant application, the structure/function relationship of many GPCRs had been investigated, several reviews on the structure/function relationship of GPCRs had been published, algorithms for predicting GPCR structure were available, and many papers that describe the engineering of GPCRs by domain swapping and mutagenesis had been published. Support for this is found in the publications listed in Exhibit B. These publications were supplied to the Office in the Information Disclosure Statement of November 5, 2007.

Given a) the vast amount of available information on structure/function relationships in GPCR proteins in general, b) the availability of the amino acid sequences of human and mouse TDAG8, c) the availability of several amino acid polymorphisms of TDAG8, as well as activating amino acid substitutions; and d) the structure/function information on TDAG8 in the instant specification, the Applicant submits that one of skill in the art would be able to envision a large number of operable variants of TDAG8.

The Applicant understands that the effect of amino acid and nucleotide substitutions cannot be predicted with absolute certainty. However, given the information in the instant specification and the deep general understanding of the structure and function of GPCR proteins, the Applicant submits that such molecules are more than adequately described.

Finally, and in addition to the Applicant's prior arguments presented above, the Examiner is also referred to pages 37-42 of the current Written Description Training Materials

(see www.uspto.gov/web/menu/written.pdf). While the Applicants understand that the fact pattern described in the Training Materials is different to the fact pattern of this case, the Applicants believe that the overall teachings of the Training Materials – which indicate that claims that recite a polypeptide having at least "85% amino acid sequence identity" to a disclosed polypeptide can meet the written description requirement even if there is little knowledge about the structure/functional relationship of the polypeptide – are directly applicable to the instant case by analogy. Since there is an abundance of knowledge relating to the structure/function relationship of GPCRs, the Applicants submit that the instant claims, which recite "80% identity" language, are more than adequately described.

The Applicant submits that this rejection has been adequately addressed. Withdrawal of this rejection is requested.

Conclusion

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at (650) 833 7723.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-007CON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 11, 2007

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Enclosures:
Copies of 60/108,029 (AREN-007PRV), 60/151,114 (AREN-007PRV14) and 60/152,524 (AREN-007PRV14)
IDS to cite:

a) Zadina et al., Ann NY Acad Sci. 1999; 897:136-44 (From Aren-001CIP)

b) Silvestris et al, Enhancement of T cell apoptosis correlates with increased serum levels of soluble Fas (CD95/Apo-1) in active lupus. Lupus. 2003;12(1):8-14

c) Neurath et al, Regulation of T-cell apoptosis in inflammatory bowel disease: to die or not to die, that is the mucosal question. Trends Immunol. 2001 Jan;22(1):21-6

d) Kacinski et al, Apoptosis and cutaneous T cell lymphoma. Ann N Y Acad Sci. 2001 941:194-9.

e) Malone et al, The glucocorticoid-induced gene tdag8 encodes a pro-apoptotic G protein-coupled receptor whose activation promotes glucocorticoid-induced apoptosis J. Biol. Chem. 2004 279:52850-9

Pages 37-42 of the current Written Description Training Materials (see cite on p. 10)

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